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APPLICATION NUMBER: 21036

MEDICAL REVIEW(S)

Medical Officer's Review
Original NDA (NME)

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Applicant: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Drug name: Zanamivir (Relenza®, GR121167X, GG167, 5-acetylamino-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2enoic acid)

Dosage form: Inhaled dry powder

Route of administration: Inhalation

Proposed indication: Treatment of influenza A and B

Related INDs: IND
IND
IND

Related minutes/letters: Teleconference on pre-NDA issues June 25, 1998
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I. Resume

In support of safety and efficacy of inhaled dry powder zanamivir for treatment of influenza, the applicant has submitted results of three adequate and well-controlled clinical trials with endpoints based on temperature recordings and symptom scores. The application provides additional safety and activity data from challenge studies and phase 2 treatment and prophylaxis studies, and a preliminary report of a phase 3 community prophylaxis trial. The principal treatment studies included adults and adolescents (aged 12 years and over). Information on younger children in the original NDA submission included one single-dose phase 1 study and several compassionate use case summaries. Later in the course of review, limited safety information was also made available from ongoing treatment investigations in pediatric patients.

The three principal phase 3 treatment trials provide comparisons of zanamivir 10 mg twice daily for five days against placebo (the lactose powder vehicle which is also present in the drug preparation) in patients with acute influenza-like illness, with confirmation of influenza by culture, serology, and investigational direct tests. All study subjects received instruction in the use of the inhaled dry powder preparation and were judged stable enough at study entry to be expected to complete outpatient treatment. All three studies entered subjects within 36 to 48 hours after onset of symptoms. The primary outcome measure was time to the first occurrence of temperature below 37.8 C with no feverishness and no more than mild cough, headache, myalgia, and sore throat, maintained for a further 24 hours, with measurements obtained at half-day intervals. The primary analysis was performed using subjects with at least one positive diagnostic test for influenza. The largest phase 3 treatment study (conducted in the US and Canada) did not show a convincing treatment effect, with a point estimate of difference between treatment groups in median time to the primary endpoint of marginal clinical importance (one day) and a p value greater than .05. Secondary endpoints including time to return to normal activities and time to alleviation of major symptoms (as defined above) without ongoing use of the protocol-provided standard acetaminophen and cough suppressant relief medications showed smaller or no treatment effect in this study. However, among the secondary analyses prospectively considered important, some analyses including investigator's post-treatment assessment of severity of illness did suggest possible differences between treatment groups. Several alternative approaches to the primary endpoint (such as exclusion of subjects positive for influenza on polymerase chain reaction without positive culture or serology) yielded slightly lower p values with point estimates similar to the primary analysis. Subjects defined as "high-risk" in this study (elderly, or underlying respiratory or cardiac disease) had a negative point estimate for treatment effect (median time to primary endpoint longer on zanamivir than placebo), as did the respiratory and cardiac subgroups of the high-risk population. Subjects with no test positive for influenza also had a negative point estimate for treatment effect. In contrast, the two smaller phase 3 studies showed larger treatment effects with smaller p values. Positive treatment effects in these two studies were also seen on multiple secondary analyses and subgroup analyses. Attempts to find differences in the study populations or process that would explain the different results did not yield a definitive

answer but focused on dissimilarities in use of symptomatic relief medications and (anecdotal) possible differences in regional familiarity with the device/delivery system, which was found to present some challenges in first-time use without hands-on instruction. Several phase 2 studies, which enrolled smaller numbers of subjects, recorded symptoms for shorter time periods, and/or used zanamivir regimens different from the proposed marketed regimen, were used for supporting information but did not fully resolve issues raised by the discrepancies between results in the principal phase 3 treatment studies.

Frequencies of most clinical and laboratory adverse events were similar in zanamivir and placebo recipients. Because placebo recipients inhaled the same lactose powder present as a vehicle in the active drug preparation, it was not possible to determine whether some gastrointestinal, respiratory, and ENT adverse events might be attributable to the drug/vehicle combination, but most events were mild and not treatment-limiting. One adverse event of potential concern was the occurrence of reproducible bronchospasm (as measured by decline in FEV1), after zanamivir but not after placebo, in one of 13 asthmatic patients in a phase 1 safety and tolerability study; however, aggregate PFT results for all subjects in the study did not show clinically meaningful drug effects. Changes in drug susceptibility during treatment were not detected in the phase 3 studies but could not be ruled out because of the lack of a rèliable cell-culture-based system for surveillance and the use of relatively insensitive sampling methods (throat swabs) for monitoring; one instance of viral mutation to a drug-resistant variant (involving mutations in both the hemagglutinin and the neuraminidase) was reported in an immunocompromised patient receiving an investigational nebulized preparation of zanamivir.

This application was reviewed on a Priority basis and was presented to the Advisory Committee on February 24, 1999. During the Advisory Committee discussion, some panelists indicated that the drug should be viewed as an advance in influenza therapy, but concerns were expressed about a number of issues including the equivocal treatment effect in the largest (and North American) phase 3 treatment study, the most appropriate principal measure of treatment effect including concerns about possible recurrence of symptoms after reaching the primary endpoint, the limited amount of virologic information in the application, the limited amount of information in highest-risk patients, and potential difficulties in use of the device/delivery system by uninstructed patients in the setting of acute illness. The Committee panelists voted 13 to 4 against recommending approval of the drug at that time based on the information presented to them.

Following discussions with the review team in the aftermath of the Advisory Committee meeting, the applicant provided additional analyses, data, and proposals for follow-up to some of the concerns raised by the panelists. Updated Chemistry, Manufacturing, and Controls information was submitted as an amendment to the NDA shortly after the Advisory Committee meeting and was considered to be a major amendment extending the review timeline. Other information submitted during the follow-up period included additional analyses of treatment effects in patient subgroups that could be defined

uniformly across the principal studies; analyses of secondary endpoints including provisions for assessing symptom recrudescence after the primary endpoint and analyses more similar to those employed in studies of previously approved anti-influenza drugs; quantitative virology summaries and a proposal for surveillance of resistance emergence; interim safety and pulmonary function data from ongoing studies of prophylaxis in nursing home residents and treatment in patients with underlying respiratory disease; and proposals (and pre-test results) for improvement and assessment of patient instruction materials. These additional submissions were taken into account in ongoing review, in consideration of the extent to which Advisory Committee concerns had been addressed, in discussion of possibilities for labeling language in the event of approval, and in formulation of Division recommendations to be submitted for higher-level CDER review. Concerns from the initial phases of review, from the Advisory Committee proceedings, and from other discussions were considered in terms of whether they could be adequately addressed by the additional information received, by labeling language, and by phase 4 commitments.

Labeling discussions were initiated early in the review period. Division concerns about the inconclusive results of the largest Phase 3 study and about device use were communicated and discussed with the applicant, also beginning early in the review period and continuing before and after the Advisory Committee discussions. Internal discussions, after examination of data in the original NDA submission and amendments received up through June, addressed these issues and others raised in the Advisory Committee deliberations and in comments from internal consultants. When the available data were taken together and considered in the perspective of other known influenza studies and drugs available for influenza, the predominating conclusion was that approval could be justified if, and only if, several conditions were satisfied. One condition was that label language should reflect the modest nature of the evidence for treatment effect and the modest magnitude of apparent treatment effect in the target population (without suggesting that the most extreme positive results in other populations could be applied to this population) and describe precautions regarding selection of patients and potential risks of adverse events in those with underlying respiratory disease. A second condition was that phase 4 commitments should be clearly set out to provide for increasing the available information regarding clinical and microbiological efficacy and safety outcomes. A third was that attention should be devoted to emphasizing and improving the instruction process. All of these considerations were communicated to the applicant and incorporated into ongoing discussions of labeling and phase 4 commitments. The NDA was approved on July 26, 1999, with package insert Indications and Usage wording "RELENZA is indicated for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. This indication is based on studies in which the predominant influenza infections were influenza A, and a limited number of patients with influenza B were also enrolled (see Description of Clinical Studies and PRECAUTIONS)."

II. Regulatory Background

The original IND for zanamivir was submitted

The drug is described as an inhibitor of influenza virus neuraminidase ("an analogue of sialic acid that inhibits neuraminidase by associating tightly with its sialic acid binding site": section 2.2.5 of Microbiology Summary, p. 202, volume 1 of NDA 21-036) with activity against influenza A and B in vitro and in animal studies (see Microbiology and Pharmacology/Toxicology reviews). The drug appears to have little bioavailability after oral ingestion (see Biopharmaceutics review for discussion of distribution and pharmacokinetics after various routes of administration). Development in human studies has been pursued using intranasal or orally inhaled administration (a nebulized preparation has also been used to a limited extent, principally for compassionate use, and intravenous administration has been employed in a few phase 1 studies).

An end-of-phase-2 meeting on May 1, 1997, focused on the sponsor's plan to pursue studies of the inhaled dry powder preparation, with drug delivered using a lactose powder vehicle for oral inhalation with a delivery device (the Diskhaler) also used with corticosteroid and bronchodilator preparations for chronic treatment of asthma. The end-of-phase-2 briefing document and discussions at the end-of-phase-2 meeting referred to proposed studies of inhaled dry powder zanamivir for symptomatic treatment of naturally acquired influenza.

[redacted]

The application was reviewed on a Priority basis, with an initial target date of April 27, 1999, which was extended to July 27, 1999 on the basis of a major amendment of March 2, 1999, in accordance with the regulatory procedures for extension of review timelines following receipt of major amendments during the review process.

Published studies of human use of zanamivir include reports from phase 1 challenge studies (JAMA 1996;275:295-299, J Infect Dis 1997;176:1417-1422) that indicated that the intranasal preparation reduced the incidence of disease, the duration of viral shedding, and the occurrence of middle ear pressure abnormalities when used for prophylaxis or early treatment of experimental influenza A infection of volunteers. A publication summarizing two phase 2 treatment studies (N Engl J Med 1997;337:874-880) suggested a decrease in time to alleviation of symptoms in previously healthy adults with laboratory-confirmed acute influenza. A publication describing a phase 3 study in the

Southern Hemisphere (Lancet 1998;352:1877-1881) suggested similar results. One report describing emergence of zanamivir-resistant influenza B virus in an immunocompromised child has appeared (J Infect Dis 1998;178:1257-1262). Results from a prophylaxis study in university communities were published late in the review process for this NDA (JAMA 1999;282:31-35), and results from another phase 2 study using inhaled plus intranasal zanamivir (J Infect Dis 1999;180:254-261) and from a phase 1 challenge study using intravenous zanamivir (J Infect Dis 1999;180:586-593) were published shortly after the end of the review period.

III. Phase 3 Placebo-Controlled Clinical Treatment Trials

The three principal Phase 3 studies submitted in this NDA can be briefly outlined as follows. In all three studies, a five-day treatment course of inhaled dry powder zanamivir, 10 mg twice daily, was compared against a placebo consisting of the lactose powder vehicle which is also present in the zanamivir preparation. For entry, subjects were required to have at least two major symptoms of influenza-like illness plus either subjective feverishness or measured temperature elevation. The symptom course over time was measured using diary cards, with additional assessments by study staff at baseline and after treatment.

The attempt to enroll subjects at risk of complications was considered an important feature of these studies. High-risk subjects were defined in these protocols as including those aged 65 or over and those with specified underlying respiratory or cardiac disease (inclusion of subjects with renal disease, metabolic disease, or immune compromise differed between studies; respiratory disease as a high-risk criterion was "chronic respiratory disease requiring regular medication" in case report forms for all three studies). However, because enrollment required judgments by the investigator that satisfactory completion would be achieved, including an expectation that the subject would successfully complete the study as an outpatient, patients who were particularly frail or had multiple complex medical problems would not be expected to be heavily represented. In all three studies, ability to use the drug/device preparation satisfactorily was a requirement for enrollment, standard instructions on how to teach subjects to use the device were supplied to study centers, and the first dose was administered under supervision at the study site at the time of enrollment, with the subject instructed to take the second dose that evening provided at least a few hours had elapsed between the first and second dose.

The primary endpoint proposed by the applicant for the principal Phase 3 studies of zanamivir was time to alleviation of major influenza-like symptoms, defined as temperature below 37.8 °C, feverishness symptom score of absent (zero), and symptom scores no greater than mild (1 on a scale of 0=absent, 1=mild, 2=moderate, and 3=severe) for cough, headache, myalgia, and sore throat, all maintained without worsening for the subsequent 24 hours. Because of the inherent subjectivity and potential imprecision of

endpoints based upon symptom scores, and because of concerns that use of ancillary medications (such as those commonly used for symptomatic relief) could confound measurement and interpretation of such endpoints, the Division has considered it important throughout development that certain important secondary endpoints (for example, reassessment of the primary endpoint with use of relief medications taken into account, and objective assessments of the subject by study personnel when available) should provide information supporting the conclusions suggested by the primary endpoint analysis. Similarly, while the prospectively defined primary analysis was time to alleviation in subjects with diagnostic tests positive for influenza, it is anticipated that any drug used for treatment of influenza will frequently be prescribed on the basis of clinical evaluations before definitive test results are available, and any such drug should not worsen the course of patients with influenza-like illness who may in fact have non-influenza viral infections.

Studies NAIA3002 and NAIB3002 were conducted in the 1997-1998 influenza season and were prospectively proposed as the two principal phase 3 treatment studies to support a treatment indication. In March 1998 the Division was informed that study NAIB3002 was severely under-enrolled (about 200 patients) due to low influenza activity in Europe, and was unlikely to complete in the 1997-1998 influenza season. It was proposed at that time that NAIA3002 and NAIB3001 (see below) would be submitted as the two principal studies in the NDA; FDA requested that if an NDA submission was anticipated with NAIB3002 (one of the two pre-designated principal studies) incomplete, interim information should be provided for review. In May 1998 the Division was informed that NAIB3002 would be submitted as a complete principal study in the original NDA, with enrollment about 350 of the prospectively planned 500.

Protocol NAIB3001 was a non-IND study conducted in the Southern Hemisphere (Australia, New Zealand, and South Africa) in the 1997 influenza season. It differed from NAIA3002 and NAIB3002 in several respects, most notably the lack of an objective temperature criterion for entry, the requirement that symptoms be present for no more than 36 hours at entry, use of different direct tests for influenza diagnosis (in addition to culture and serology which were used in all three studies), and a shorter duration of symptom recording. This study was not originally proposed as one of the two principal studies in support of the treatment indication; in March 1998, the applicant submitted serial no. 081 indicating "We have now completed initial analysis of the data from our Southern Hemisphere study NAIB3001" and proposed to submit it in lieu of NAIB3002 as a principal study, and in May 1998 the applicant indicated that NAIA3002 and NAIB3002 would be the two principal studies with NAIB3001 results included "as a source of some additional data on the safety and efficacy of zanamivir." Additional analyses (for example, time to alleviation without relief medications) not prospectively included in this protocol were performed to provide information comparable to analyses in NAIA3002 and NAIB3002.

III-A. Clinical Study NAIA3002

Protocol NAIA3002 is entitled "A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults." The draft protocol was submitted to IND [redacted] The study report is located in volumes 102 through 108 of NDA 21-036.

III-A1. NAIA3002 Study Design

This study was conducted in North America and was designed to evaluate efficacy and safety/tolerability of inhaled zanamivir compared to placebo (lactose powder vehicle) in treatment of symptomatic influenza virus infections in patients aged 12 years and over. The primary efficacy endpoint, termed time to alleviation of major symptoms, was defined as no fever or feverishness and other symptoms none or mild, maintained for a further 24 hour period. The study was also designed specifically to address efficacy and safety in "high-risk" patients. Enrollment of approximately 25% "high-risk" subjects was projected. Enrollment required temperature at least 37.8° C and at least two of the four designated symptoms (headache, myalgia/arthralgia, sore throat, cough) present for no more than two days at a time when influenza was documented to be circulating in the community. The influenza-positive subpopulation was defined as those having a positive result on culture, serology (fourfold rise in antibody titer), or an investigational direct test using polymerase chain reaction (PCR). Vaccinated subjects could be enrolled if they had a positive rapid test for influenza. Ability to use the Rotadisk/Diskhaler system was an inclusion criterion and the first dose of study drug was administered under supervision/instruction at the study site, with the subject instructed to take a second dose later that day if the interval between the first two doses was at least two hours; subsequently, subjects were to take two doses per day (each dose consisting of two 5 mg zanamivir/20 mg lactose, or 20 mg lactose placebo, inhalations) to a total of five days of therapy. Temperature and symptoms, and other items such as use of standard symptom-relief medications (acetaminophen and cough suppressant) were recorded by the subject on a diary card for 14 days, and subjects still symptomatic at 14 days were to record symptoms for an additional 14 days.

III-A2. NAIA3002 Efficacy Results (Summary of Applicant's Analysis)

A total of 777 subjects were enrolled (174 at Canadian and 603 at U.S. centers), of whom 365 were randomized to placebo and 412 to zanamivir. These and the following numbers are taken from Clinical Study Report (CSR) Tables 1-8. A total of 109 subjects (14%) were designated as "high-risk." In the placebo group, 6% discontinued the study prematurely (2 adverse events, 2 "consent withdrawn", 15 lost to follow-up, 1 protocol violation, 1 "other"); in the zanamivir group, 5% discontinued prematurely (5 adverse events, 2 "consent withdrawn", 13 lost to follow-up, 1 "other"). In each group, 4%

discontinued study medication early, with the reason given as adverse event for 2% in each group (6 placebo and 9 zanamivir subjects). Protocol violations were identified in 13% of placebo and 10% of zanamivir subjects, the most common being inclusion criterion 3 (first dose of medication on first or second day of symptoms; 4% in each group) and post-treatment visit delayed past day 8 (3% of placebo, 2% of zanamivir subjects) or lacking (4% of placebo, 3% of zanamivir subjects). Demographic data were reasonably balanced between treatment groups; 54% of the placebo group and 50% of the zanamivir group were female, while 84% of the placebo group and 87% of the zanamivir group were classified in the study report as White, and 21% in each group were classified as current smokers. About one-quarter of subjects (28% placebo, 22% zanamivir) were recorded as taking concurrent anti-infective/immunological drugs, principally macrolides, penicillins, or cephalosporins, while 10% (12% placebo, 9% zanamivir) were recorded as taking concurrent beta-agonists. Of all randomized subjects, 14% (15% placebo, 13% zanamivir) had received current season influenza vaccine (CSR Table 9). Overall, 569 subjects were considered to have confirmed influenza. Sources of influenza diagnosis are summarized in the Table III-A2a below (data from CSR Table 10: here and in the remainder of the review, "CSR Table" refers to a table in the Clinical Study Report in the NDA serving as a data source; ST before the number of a CSR table refers to a table in the Supporting Tables section of the CSR. Tables compiled for this review are numbered according to the section of the review in which they appear.). Overall influenza symptom scores at baseline were reasonably balanced between treatment groups (CSR Table 11).

Table III-A2a. Influenza diagnosis in NAIA3002

Influenza diagnosis	Placebo	Zanamivir
Total subjects	365	412
Positive for influenza A	251 (69%)	307 (75%)
Positive for influenza B	5 (1%)	3 (<1%)
Influenza positive, type unknown	1	2
Positive by culture	172/364	221/411
Positive by PCR	238/355	291/404
Positive by serology	169/296	211/347

Selected outcome measures are summarized in Table III-A2b below. ITT denotes the Intent-to-Treat population (all randomized subjects). In sensitivity analyses (CSR Supporting Tables ST1-8), censoring patients with incomplete data produced a lower p value (no change in medians) for time to alleviation in the influenza positive population, but high-risk subjects (ITT or influenza positive) still showed longer times to alleviation in the zanamivir than the placebo group using either the median or the mean as a descriptor. Restricting the definition of "influenza positive" to positive culture and/or serology (ST10) also yielded unchanged medians and a lower p value (.045) for time to alleviation, while the small number of subjects (34 placebo, 24 zanamivir) positive only on PCR had a longer median time to alleviation in the zanamivir group (5.75 vs 5.0 days (ST11)). In subgroup analyses (CSR supporting tables 16 and 20), treatment effect in influenza positive subjects did not vary appreciably by gender (1.0 day difference in medians for female subjects, 1.25 day difference for male subjects) or vaccination status but was inconsistent across age groups (point estimates of difference in medians largest